PATENT SPECIFICATION

Application Date: April 20, 1937. No. 11220/37. 493,948

Complete Specification Left: May 20, 1938.

Complete Specification Accepted: Oct. 18, 1938.

PROVISIONAL SPECIFICATION

Improved Method of High Vacuum Distillation

We, KODAK LIMITED, a Company registered under the Laws of Great Britain, of Kodak House, Kingsway, London, W.C.2, do hereby declare the nature of this invention, which has been communicated to us by Eastman Kodak Company, a Company organised under the Laws of the State of New Jersey, United States of America, of 343, State Street, Rochester, New York, United States of America, to be as follows:—

This invention relates to an improved method of high vacuum distillation, particularly of vitamins, sterols, hormones and other substances possessing similar therapeutic properties. The invention has special reference to the process of high vacuum-short path distillation which is generic to that particular form of distillation known as "molecular" distillation. High vacuum-short path distillation is said to be "molecular" when the distance separating evaporative and condensing surfaces is equal to or less than the mean free path of the molecules of the substance being distilled.

As is well known certain vitamins are liable to heat and readily suffer decomposition with consequent loss of their therapeutic qualities. In our copending application 27534/36 (Serial No. 476,134) we have already proposed in the molecular distillation of a distilland containing vitamins, sterols or hormones to add a carrier liquid which has a boiling point in the neighbourhood of a particular fraction of the distillate desired. This liquid facilitates the molecular distillation, and often allows it to be performed at a lower temperature.

According to this invention, when it is desired to collect a plurality of fractions from any one substance, carrier liquid or liquids, is or are added to the distilland, capable of producing distillate fractions equivalent in number to the number of distillate fractions obtained from the material being distilled, these distillate fractions from the carrier liquid having the further property of being easily separated from the distillate fractions of the substances under investigation.

The carrier liquids facilitate the high vacuum-short path and in particular molecular distillation of the fractions with which they are associated as fractional distillates.

One preferred carrier is an oil which is a mixture of components, having different boiling points such that one of these components will distil with say, a low boiling fraction, one with say, a medium boiling fraction and one with say a high boiling fraction. It is an essential feature of this process that the diluent oil whether complete or resolved into its various constituent fractions, shall be readily removed from the substances desired, without damage to them. The process of removal may be effected by either physical or chemical means. One carrier oil may be used for each component or again, one particular diluent oil may contain components of such varying boiling points as to replace the necessity of adding several carrier oils.

The following examples, whilst not limiting the scope of the invention, will illustrate the manner in which it may be performed.

EXAMPLE 1.

In the distillation of sterol-containing oils to obtain fractions consisting substantially of cholestane and stigmasterol respectively, a carrier liquid consisting of a mixture of tripalmitin and tricaproin or dicaproin monopalmitin is added to the distilland and the cholestane distilling at substantially the same temperature as the tricaproin or dicaproin monopalmitin and the stigmasterol distilling with the tripalmitin. The distillate fractions are then saponified when in the first case the tricaproin or dicaproin monopalmitin is converted to a soap and can be readily removed by solution in water and extraction of the non-saponifiable matter with ether and repeated washing with water etc., and likewise in the second case tripalmitin is converted to Na tripalmitate, and the saponifiable and non-saponifiable fractions can be readily separated as before. By use of these readily removable carrier oils, valuable vitamin, sterol and hormone

concentrates can be obtained without their suffering undue damage during the distillation process.

EXAMPLE 2.

In the separation of free Vitamin D from Vitamin A esters, mono-caproin dipalmitin may be added to the distilland and will distil with the free Vitamin D fraction and triolein may be added to the distilland to distil with the Vitamin A esters. The glycerides may be removed later by saponification etc. as in Example 1.

EXAMPLE 3.

To facilitate the separation of benzpyrene from cholesteryl butyrate by molecular distillation oleic acid is added to the distilland to distil with the benzpyrene and triolein is added to distil with the cholesteryl butyrate. On subsequent distillation with fractionation and neutralisation of the distillates, alkaline oleate can readily be separated from the benzpyrene and alkaline triolcate and alkaline butyrate can be separated from the cholesterol.

EXAMPLE 4.

In the separation by distillation of the substances anthracene, cholesterol and digitogenin, the addition of constant yield oil (as described in application 18759/36) to the distilland facilitates the separation of these three substances.

EXAMPLE 5.

In the separation of indigo from Di brom indigo, it is advantageous to add dicaproin monopalmitin to the mixed distilland which will distil with the indigo and to add triolein to distil with the di-brom-indigo. After distillation the respective distillate fractions are saponified as in previous examples.

Broadly speaking it will be seen that esters are the most suitable carrier liquids, while mineral oils are usually unsuitable on account of the difficulty of separation.

By adding to the distilland a carrier liquid or liquids capable of distilling over in a plurality of fractions each accompanying a desired fraction of potent material, there is no necessity to distil a carrier liquid unaccompanied by desired fractions (except in example 4) and thus the load on the still is reduced. Intermediate flushing of the condensing surfaces with a readily separable liquid may be employed to avoid contamination of one fraction by the preceding fraction.

It will be apparent that whilst carrier oils distilling at the same temperature as the required distillate fraction will continue to distil after the majority of the distillate required fraction has been condensed and will therefore assist in flushing the condensing surface, carrier oils having a boiling point slightly above that of the required distillate may also be used with advantage, since they will be evolved individually and will sweep the substance from the still and simultaneously clean the condensing surface.

Dated this 19th day of April, 1937.

W. P. THOMPSON & CO.,
12, Church Street, Liverpool, 1.
Chartered Patent Agents.

COMPLETE SPECIFICATION

Improved Method of High Vacuum Distillation

We, KODAK LIMITED, a Company registered under the Laws of Great Britain, of Kodak House, Kingsway, London, W.C.2, do hereby declare the nature of this invention, which has been communicated to us by Eastman Kodak Company, a Company organised under the Laws of the State of New Jersey, United States of America, of 343, State Street, Rochester, New York, United States of America, and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

This invention relates to an improved method of high vacuum distillation of organic materials and has particular reference to the distillation of vitamins, sterols, hormones and other substances possessing valuable therapeutic properties. High vacuum distillation is defined as distillation taking place at a pressure below 10 mm. mercury. When the distance separating distilling and condensing surfaces is somewhat greater than the mean free path of the molecules of the distilland and when the distillation pressure is in the neighbourhood of 0.0 mm. Hg. and preferably less, then this form of distillation is known as high vacuum-short path distillation. Molecular distillation comprises a specific form of high vacuum-short path distillation in that not only does an unrestricted space exist between the distilling and condensing surfaces as above but the actual distance separating distilling and condensing surfaces is equal to or less than the mean free path of the molecules of the distilland and the distillation process is preferably carried out at pressures over the range 0.0001 mm. Hg. to 0.00001 mm. Hg.

It is known that therapeutic substances such as vitamins are extremely liable to heat and readily suffer decomposition with consequent loss of their therapeutic pro-

parties. This factor becomes particularly important in those instances where the vitamins or other desired substances are present only in small quantities and it is desired to separate them from the main body of the distilland as completely as possible. It has already been proposed in our patent specification No. 473,194 to add a carrier liquid to the distilland containing vitamins sterols or hormones, such carrier liquid having a boiling point in the neighbourhood of a particular distillate fraction, thereby distilling at the same time as the particular distillate fraction and facilitating the latter's removal from the distilland, not only more completely but very often at a lower temperature. It has also been proposed in our patent specification No. 482,831 to add to the distilland, a synthetic mixture compounded so as to give a constant or known amount of distillate for each uniform increase in temperature.

According to the present invention, a plurality of distillate fractions are obtained by distillation of any particular organic substance by using one or more carrier liquids capable of yielding distillate fractions equivalent in number to the number of distillate fractions required from the substance and of which one distils contemporaneously with each of the desired fractions. The distillate fractions from the one or more carrier liquids must have the further property of being easily separated from the desired fractions, either by physical or chemical means. Thus, if it is desired to collect two specific distillate fractions from a particular raw material, a carrier liquid is added to the distilland which itself provides two fractions distilling contemporaneously with the desired fractions.

In a modification of the invention, the number of carrier liquids or of carrier liquid fractions may be increased in order to provide one or more intermediate fractions serving as flushing liquids prior to and/or subsequent to the distillation of the desired fractions.

It is an essential feature of this process that the diluent oil whether complete or resolved into its various constituent fractions, shall be readily removed from the substances desired, without damage to them.

The choice of carrier liquid or liquids will depend upon the nature of the distilland to which it is to be added. Very closely related substances cannot usually be easily separated and therefore should be avoided. When distilling a distilland in order to separate non-saponifiable materials as distillate, one can, with advantage, employ an added oil which is saponifiable. The distillate obtained would then be a mixture of the desired non-saponifiable distillate and saponifiable carrier liquid fractions. The carrier liquid fractions can then be separated in a simple manner by saponification with separation of the non-saponifiable material. When distilling substances such as vitamins, hormones, sterols, which are non-saponifiable, this expedient can be used with considerable advantage.

Added carrier liquids may be used which are easily separable by methods other than chemical separation, for instance a decidedly satisfactory oil would be one which is miscible with the distilland and distillate at elevated temperatures but immiscible therewith at low temperatures. This material could be added to the distilland and, upon distillation, a mixture of distillates would be obtained which could be readily separated by mere cooling or super-cooling followed by filtration. Other methods of separation, such as by partitioning in differential solvents, or by fractional crystallisation, are to be understood as being contemplated and within the scope of this invention.

One carrier oil may be used for each component or again, one particular diluent oil may contain components of such varying boiling points as to avoid the necessity of adding several carrier oils.

The following examples, whilst not limiting the scope of the invention, will illustrate the manner in which it may be performed.

EXAMPLE 1.

In the distillation of sterol-containing oils to obtain fractions consisting substantially of cholestane and stigmasterol respectively, a carrier liquid consisting of a mixture of tripalmitin and tricaproin or dicaproin monopalmitin is added to the distilland the cholestane distilling at substantially the same temperature as the tricaproin or dicaproin monopalmitin and the stigmasterol distilling with the tripalmitin. The distillate fractions are then saponified when in the first case the tricaproin or dicaproin monopalmitin is converted to a soap and can be readily removed by solution in water and extraction of the non-saponifiable matter with ether and repeated washing with water etc., and likewise in the second case tripalmitin is converted to Na tripalmitate, and the saponifiable and non-saponifiable fractions can be readily separated as before. By use of these readily removable carrier oils, valuable vitamin, sterol and hormone

concentrates can be obtained without their suffering undue damage during the distillation process.

EXAMPLE 2.

In the separation of free Vitamin D from Vitamin A esters mono-caproin dipalmitin may be added to the distilland and will distil with the free Vitamin D fraction and triolein may be added to the distilland to distil with the Vitamin A esters. The glycerides may be removed later by saponification as in Example 1.

EXAMPLE 3.

To facilitate the separation of benzpyrene from cholesteryl butyrate by molecular distillation, olein acid is added to the distilland, to distil with the benzpyrene and triolein is added to distil with the cholesteryl butyrate. On subsequent distillation with fractionation and neutralisation of the distillates, alkaline oleate can readily be separated from the benzpyrene and alkaline triolate and alkaline butyrate can be separated from the cholesterol.

EXAMPLE 4.

In the separation of indigo from di-brom indigo, it is advantageous to add diacpropin monopalmitin to the mixed distilland which will distil with the indigo and to add triolein to distil with the di-brom-indigo. After distillation the respective distillate fractions are saponified as in previous examples.

Broadly speaking it will be seen that esters, and particularly esters of high molecular weight aliphatic fatty acids, are the most suitable carrier liquids, while mineral oils are usually unsuitable on account of the difficulty of separation.

By adding to the distilland a carrier liquid or liquids capable of distilling over in a plurality of fractions each accompanying a desired fraction of potent material, there is no necessity to distil a carrier liquid unaccompanied by desired fractions and thus the load on the still is reduced. Intermediate flushing of the condensing surfaces with a readily separable liquid may be employed to avoid contamination of one fraction by the preceding fraction.

Such flushing is however preferably effected by a particular component of the carrier liquid, i.e. by one or more of the plurality of fractions contained within the carrier liquid and is readily separable from the desired distillate by saponification or other means.

It will be apparent that whilst carrier oils distilling at the same temperature as the required distillate fraction will continue to distil after the majority of the distillate required fraction has been condensed and will therefore assist in flushing the condensing surface, carrier oils having a boiling point slightly above that of the required distillate may also be used with advantage, since they will be evolved individually and will sweep the substance from the still and simultaneously clean the condensing surface.

Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. A process of high vacuum distillation of organic substances which may contain only a small amount of desired substances to obtain two or more fractions, which comprises adding to the distilland one or more carrier liquids which on distillation yield the same number of fractions, of which one distils contemporaneously with each of the desired fractions but is readily separated therefrom.

2. A process as claimed in claim 1, carried out under conditions pertaining to high vacuum-short path and particularly molecular distillation.

3. A process as claimed in claims 1 or 2, in which a naturally-occurring carrier liquid is used, comprising therein several components of differing volatility.

4. A process as claimed in claims 1 or 2 in which two or more esters comprise the carrier liquids.

5. A modification of the process as claimed in any of the preceding claims in which the number of carrier liquid fractions is increased so that one or more intermediate fractions serve as flushing media prior to and/or subsequent to the distillation of one or more desired fractions.

Dated this 19th day of May, 1938.

W. P. THOMPSON & CO.,
12, Church Street, Liverpool,
Chartered Patent Agents.

Leamington Spa: Printed for His Majesty's Stationery Office, by the Courier Press.—1938.